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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,949	NAKASHIMA ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8-10,13 and 14* is/are rejected.

7)☒ Claim(s) *4-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed on August 7, 2006 is acknowledged and has been entered. Claims 1, 2, 4, 5, and 13 have been amended. Claim 3 has been cancelled. Accordingly, claims 1, 2, 4-10, 13, and 14 are pending and are under examination.

Withdrawn Rejections

2. The rejections of claim 3 are now moot in light of Applicant's cancellation of the claim.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. Claims 1, 2, 4-10, 13, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in failing to clearly define what antigen or antibody in the whole blood sample is being assayed for. In this case, claim 1 was amended to remove that the antigen or antibody is present in the plasma component of the [anticoagulated] whole blood sample. Accordingly, it is unclear as to whether the target antigen or antibody encompasses cell surface antigens and intracellular antibodies present in the

blood cell component of the whole blood sample. Perhaps, the target antigen or antibody should be recited as "soluble target antigen or antibody" in the preamble and in the body of the claim, in order to define that the target antigen or antibody refers to those present in the plasma portion of the whole blood sample.

Claim 1, step d) as amended is ambiguous in failing to define how the concentration of the target antigen or antibody is being obtained. Step d) merely recites "distinguishing and counting the unagglutinated insoluble carrier particles, the agglutinated insoluble carrier particles, and the blood cells from the intensity of the scattered light ..., in reference to the first and second threshold values ..., so as to obtain a concentration...[and] *based on* the number of agglutinated insoluble carrier particles and the unagglutinated insoluble carrier particles", but has not clearly recited, defined, nor provided how the concentration is being obtained or measured in this immunoassay method. Specifically, how is the concentration of the target antigen or antibody obtained, based on the number of agglutinated insoluble carrier particles and unagglutinated insoluble carrier particles, and what then is the significance of having distinguished and counted the blood cells in this instant step? Does Applicant intend that the number of the agglutinated insoluble carrier particles directly provide the concentration of target antigen or antibody?

Claim 1, step e) is also ambiguous in reciting, "correcting the concentration ... according to the number of blood cells" because it fails to specifically define how the concentration of the target antigen or antibody is being corrected, in relation to the blood cells, in this immunoassay method.

Claim 1 is, therefore, incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Claim 5 is indefinite in failing to clearly define what antigen or antibody in the whole blood sample is being assayed for. In this case, claim 5 was amended to remove that the antigen or antibody is present in the plasma component of the [anticoagulated] whole blood sample. Accordingly, it is unclear as to whether the target antigen or antibody encompasses cell surface antigens and intracellular antibodies present in the blood cell component of the whole blood sample. Perhaps, the target antigen or antibody should be recited as "soluble target antigen or antibody" in the preamble and in the body of the claim, in order to define that the target antigen or antibody refers to those present in the plasma portion of the whole blood sample.

Claim 5, step d) is ambiguous in failing to define how the concentration of the target antigen or antibody is being obtained. Step d) merely recites "distinguishing and counting the unagglutinated insoluble carrier particles, the agglutinated insoluble carrier particles, and the blood cells from the intensity of the scattered light ..., in reference to the first and second threshold values ..., so as to obtain the concentration...[and] *based on* the number of agglutinated insoluble carrier particles and the unagglutinated insoluble carrier particles", but has not clearly recited, defined, nor provided how the concentration is being obtained or measured in this immunoassay method. Specifically, how is the concentration of the target antigen or antibody obtained, based on the number of agglutinated insoluble carrier particles and unagglutinated insoluble carrier particles, and what then is the significance of having distinguished and counted

the blood cells in this instant step? Does Applicant intend that the number of the agglutinated insoluble carrier particles directly provide the concentration of target antigen or antibody?

Claim 5, step e) is also ambiguous in reciting, "obtaining a mean corpuscular volume (MCV) in the whole blood sample ... [and] wherein the concentration of the target antigen or target antibody ... is corrected *according to* the MCV measurement and the number of blood cells" because it fails to specifically define how the concentration of the target antigen or antibody is being corrected, in relation to both the MCV and the number of blood cells, in this immunoassay method.

Claim 5 is, therefore, incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

All comments and problems identified in claims 1 and 5, apply to functional language use recitations in claims 13 and 14.

Claim 13 is indefinite in failing to clearly define what antigen or antibody in the whole blood sample is being assayed for using the apparatus. In this case, claim 13 was amended to remove that the antigen or antibody is present in the plasma component of the [anticoagulated] whole blood sample. Accordingly, it is unclear as to whether the target antigen or antibody encompasses cell surface antigens and intracellular antibodies present in the blood cell component of the whole blood sample. Perhaps, the target antigen or antibody should be recited as "soluble target antigen or antibody" in the preamble and in the body of the claim, in order to define that the target

antigen or antibody refers to those present in the plasma portion of the whole blood sample.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kosako (US Patent 5,527,714).

Kosako discloses an immunoassay apparatus comprising flow cell having a reaction part (mixing or agitating part) to mix an agglutination reaction mixture, a dispenser for presenting the reaction mixture to the flow cell, a laser for irradiating agglutination particles through the flow cell, a detector (photo acceptance unit) for detecting scattered light, a signal processing means having a microcomputer for converting the light signal into an electrical signal for analysis and measurement of stored digital values and for setting threshold values for distinguishing particle size distribution between agglutinated particles and unagglutinated particles. The detector is connected to an amplifier where electrical signal is converted to a digital message by an A/D converter. The apparatus further includes a data processing means (mainframe computer) for processing digital stored data (see Figure 1, column 3, lines 14-51,

column 5, lines 1-18, and column 6, lines 1-15). The apparatus also includes a calculating means (see Figure 3). Kosako specifically states in column 3, line 66 to column 4, line 4 that the immunoassay apparatus is conventional, and its construction and function is evident to one skilled in the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 2, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Kosako discloses an immunoassay comprising mixing an analyte sample with insoluble carrier particles sensitized with antibody, agitating the reaction mixture, subjecting the resulting immune agglutination reaction mixture including both agglutinated and unagglutinated particles to irradiation with laser, then nephelometrically detecting scattered light generated therefrom. The degree of agglutination is measured, and total particle size distribution curve is plotted including predetermined threshold values of unagglutinated particles, agglutinated particles, and spurious particles. The total resultant particles plotted in the distribution curve, i.e. having established threshold parameters set, include agglutinated particles, unagglutinated particles, and other (spurious) particles wherein a first size distribution of the total particles and a second size distribution of spurious particles are determined and subtracted from the first distribution to produce a corrected size distribution of insoluble particles; hence, correcting for the concentration of analyte (antigen or antibody). Therefrom, the actual concentration of antigen or antibody is obtained (see column 3, lines 27-41 and claim 1).

Kosako differs from the instant invention in failing to disclose that the analyte sample is whole blood and the spurious particles are blood cells.

Moskowitz et al. disclose an immunoassay comprising mixing a whole blood sample with insoluble carrier particles (matrix) having antigen or antibody (fibrinogen or antibody to platelet cell surface glycoprotein receptor) immobilized thereto, subjecting the resulting immune agglutination reaction mixture including both agglutinated and unagglutinated particles) to irradiation with laser light in the infrared region, then

detecting scattered light generated therefrom. A control value is used in setting a base value (threshold value) for distinguishing unagglutinated particles from agglutinated particles and a standard calibrator is used to provide a standard curve for comparison with test results. The degree of agglutination is related to the concentration of antigen or antibody in the whole blood sample. The degree of agglutination in platelets is also determined and related to the number of platelets (blood cells) (see page 6, column 2 [0069] to page 7, column 2 [0071]) and column 8 [0080]). Extent of agglutination is measured nephelometrically (light scatter) (see page 8 [0079]). The insoluble carrier particles are at least about 0.1 um – 10 um (see page 3, column 1 [0035-0039]). Desirably, the immunoassay is performed at a temperature of at least 25 °C and in the range of 30 °C-40 °C and read at a time within 10 seconds to 5 minutes (see page 8, column 1 [0078] and column 2 [0087]). Confirmation of results is performed by flow cytometry (see Figure 4 and page 10, column 1 [0123]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute whole blood as taught in the method of Moskowitz into the method of Kosako wherein agglutinated portion, unagglutinated portion, and spurious particles are taken into account for accuracy of nephelometric assay results because use of whole blood in the agglutination assay of Moskowitz has the advantage of less sample handling and the Kosako reference appears to be generic in the type of analyte mixture used which provides significant improvement in assaying for analyte in a heterogeneous sample such as whole blood.

6. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kosako (US Patent 5,527,714) in view of Moskowitz et al. (US 2001/0046685) as applied to claims 1, 2, 9, 10, 13 and 14 above, and further in view of Steel et al. (WO 98/20351).

Kosako and Moskowitz et al. have been discussed supra. Kosako and Moskowitz et al. differ from the instant invention in failing to teach that the scattered light is a forward scattered light.

Steel et al. provide that certain agglutination assays use optical flow particle analyzers that detect agglutination formation or the degree of non-agglutination by measuring forward scattered light and using particles having different sizes (see page 2, lines 6-14).

One of ordinary skill in the art at the time the invention was made would have been motivated to measure forward scattered light as taught by Steel in the nephelometric assays taught by Kosako as modified by Moskowitz for measuring degrees of agglutination because Steel specifically taught that forward scattered light has the advantage of measuring different sizes of particles and aggregation formation in an assay mixture.

Response to Arguments

7. Applicant's arguments filed August 7, 2006 have been fully considered but they are not persuasive.

A) Applicant argues that Kosako does not anticipate claims 13 and 14 because Kosako does not disclose a data processing means as recited in claim 13. Applicant

then contends that in failing to disclose a data processing means, Kosako's apparatus does not possess an element used for 1) setting a first threshold value for distinguishing unagglutinated insoluble carrier particles from agglutinated insoluble carrier particles, and a second threshold value for distinguishing the agglutinated insoluble carrier particles from blood cells based on intensity of scattered light; 2) for distinguishing and counting the unagglutinated insoluble carrier particles, the agglutinated insoluble carrier particles, and the blood cells ...; 3) for obtaining the concentration of the target antigen or the target antibody present in the whole blood ... ; and 4) for correcting the concentration of the target antigen or target antibody ... [according to] the number of blood cells.

Contrary to Applicant's argument, Kosako teaches a data processing means in column 3, lines 58-64 for use in determining soluble antigen or antibody concentration by virtue of their measured agglutination and particles size distribution as detected by light scatter signal.

In as far as Applicant's contention that Kosako fails to disclose the functional use for which the data processing means is used, i.e. 1) setting a first threshold value for distinguishing unagglutinated insoluble carrier particles from agglutinated insoluble carrier particles, and a second threshold value for distinguishing the agglutinated insoluble carrier particles from blood cells based on intensity of scattered light; 2) for distinguishing and counting the unagglutinated insoluble carrier particles, the agglutinated insoluble carrier particles, and the blood cells ...; 3) for obtaining the concentration of the target antigen or the target antibody present in the whole blood ... ;

and 4) for correcting the concentration of the target antigen or target antibody ... [according to] the number of blood cells, a recitation of the intended use of the claimed apparatus must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. To reiterate, Kosako specifically teaches the immunoassay apparatus as claimed, comprising a flow cell having a reaction and dispensing part, a laser, a detector (photo acceptance unit), a signal processing means (microcomputer) for converting the light signal into electrical signal for analysis, a data processing means (mainframe computer) for storing and processing digital data values, and a calculating means. Accordingly, Kosako is deemed to anticipate the claimed invention.

B) Applicant argues that the combination of Kosako with Moskowitz does not suggest the claimed invention because Kosako does not teach all of the elements recited in claim 1, and Moskowitz does not cure the deficiency that is lacked by the Kosako reference. Applicant specifically contends that neither Kosako nor Moskowitz teach, "setting a second threshold for distinguishing the agglutinated insoluble carrier particles from blood cells" and "distinguishing and counting the unagglutinated insoluble carrier particles, the agglutinated insoluble carrier particles, and the blood cells according to the first and second threshold values". Applicant further argues that the combination of Kosako with Moskowitz does not even teach or suggest that blood cells are counted; therefore, the step of correcting the concentration of the target antigen or

the target antibody according to the number of the blood cells, is neither taught nor suggested.

In response, the combination of Kosako with Moskowitz appears to suggest the claimed invention because Kosako provides measuring and setting thresholds for degrees of agglutination of the insoluble particles, wherein total particle size distribution curve is plotted including predetermined threshold values in order to distinguish between unagglutinated particles, agglutinated particles, and spurious particles that encompass any irrelevant component in the assay, i.e. blood cells, effects of which are intended for removal and corrected for. Such teaching appears to be consonant to currently amended claims 1 and 5, albeit very unclearly defined in the claim as to how it is actually done. The total resultant particles plotted in the distribution curve include agglutinated particles, unagglutinated particles, and other (spurious) particles wherein a first size distribution of the total particles and a second size distribution of spurious particles are determined and subtracted from the first distribution to produce a corrected size distribution of insoluble particles; hence, correcting for the concentration of analyte (antigen or antibody). Moskowitz et al. is incorporated herein, only for the teaching of using whole blood in a nephelometric immunoassay wherein whole blood sample is mixed with insoluble carrier particles having antigen or antibody immobilized thereto, subjecting the resulting immune agglutination reaction mixture including both agglutinated and unagglutinated particles, to irradiation with laser light in the infrared region, then detecting scattered light generated therefrom. Since claims 1 and 5 are so unclearly recited as to the effect of blood cell counting and its function and mechanism

by which the target antigen or antibody is corrected for, it is deemed that the combination of Kosako and Moskowitz suggests or renders obvious the claimed invention, since the language recited in claims 1 and 5, does not exclude the teaching set forth by Kosako, as applied to use of whole blood sample as suggested in the method of Moskowitz.

C) Applicant argues that the combination of Kosako and Moskowitz with Steel does not suggest the claimed invention because Steel does not cure the deficiencies of Kosako and Moskowitz wherein the combination does not disclose the first and the second threshold values as recited in the claimed invention, wherein the unagglutinated insoluble carrier particles can be distinguished from agglutinated insoluble carrier particles, or that the agglutinated insoluble carrier particles can be distinguished from blood cells, and that counting the particles or blood cells can be based on the set thresholds.

In response, the combination of Kosako with Moskowitz indeed, suggests the claimed invention because Kosako provides measuring and setting thresholds for degrees of agglutination of the insoluble particles, wherein total particle size distribution curve is plotted, including predetermined threshold values in order to distinguish between unagglutinated particles, agglutinated particles, and spurious particles, that encompass any irrelevant component in the assay, i.e. blood cells, the effects of which are intended for removal and corrected for. Such teaching appears to be consonant to currently amended claims 1 and 5, albeit very unclearly defined in the claim, as to how

the method is actually done. On the other hand, Moskowitz et al. teaches application of whole blood in a nephelometric assay wherein whole blood sample is mixed with insoluble carrier particles having antigen or antibody immobilized thereto, and wherein the resulting immune agglutination reaction mixture including both agglutinated and unagglutinated particles is subjected to irradiation with laser light in the infrared region, and then intensity of scattered light is generated therefrom. Steel is incorporated herein, only for the teaching of using forward scattered light in detecting particles in the flow cell. Hence, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teaching of Steel into the nephelometric method of Kosako as modified by Moskowitz because Steel specifically taught application of forward angle scatter measurements in detecting agglutination formation or degrees thereof, and both of Kosako and Moskowitz teach nephelometric assays involving distinguishing between particle sizes in agglutination reactions and light scatter measurements.

Prior Art

8. Claims 4-7 are clear of the prior art. Claims 4-7 would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
October 24 , 2006